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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
TURNER, SHARON L	

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 07/13/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/897,438	MIKOSHIBA ET AL.	
	Examiner	Art Unit	
	Sharon L. Turner	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 April 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *4-8,10 and 11* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *4-8 and 10-11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *03 July 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 4-30-04 has been entered.

2. The amendment filed 3-1-04 has been entered into the record and has been fully considered.

3. The text of Title 35 of the U.S. Code not reiterated herein can be found in the previous office action.

4. As a result of Applicant's amendment, all rejections not reiterated herein have been withdrawn by the Examiner.

Election/Restriction

5. Applicant's election of Group II, claims 4-8 and 10-11 in part in Paper No. 8 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

6. Claims 1-3 and 9 are canceled. Claims 4-8 and 10-11 are pending.

Claim Rejections - 35 USC § 112

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly

connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 4-8 and 10-11 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification describes a polypeptide sequence consisting of SEQ ID NO:2. However, the claims as written are directed to polynucleotides encoding polypeptides comprising a CR-50 antibody recognition site of Reelin protein and neither a F-spondin domain nor a repeat site, comprising SEQ ID NO:2 and neither a F-spondin domain nor a repeat site, polypeptides as above comprising a deletion, substitution or addition of one or more amino acids, polypeptides encoded by degenerative nucleic acids and wherein the polypeptide binds to antibody CR-50. Additionally the claims recite compositions that stimulate the assembly of Reelin protein and that are useful for diagnosis and/or treatment of diseases resulting from abnormally positioned neurons which comprise the aforementioned nucleic acids. However, the instant disclosure of a single polypeptide, that of SEQ ID NO:2, and a single nucleic acid encoding it (SEQ ID NO:1) does not adequately support the scope of the claimed genus, which encompasses a substantial variety of subgenera. A genus claim may be supported by a representative number of species as set forth in *Regents of the University of California v Eli Lilly & Co,* 119F3d 1559, 1569, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997), which states:

"To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention". Lockwood v. American Airlines, Inc., 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); In re Gosteli, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1980) ("[T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed.") Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." Lockwood, 107 F.3d 1565, 1572, 41 USPQ2d at 1966.

An adequate written description of a DNA, such as the cDNA of the recombinant plasmids and microorganisms of the '525 patent, "requires a precise definition, such as by structure, formula, chemical name, or physical properties," not a mere wish or plan for obtaining the claimed chemical invention. Fiers v. Revel, 984 F.2d 1164, 1171, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993). Accordingly, "an adequate written description of a DNA requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it; what is required is a description of the DNA itself." Id at 1170, 25 USPQ2d at 1606."

A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus, or of a recitation of structural features common to the genus, which features constitute a substantial portion of the genus. The instant specification discloses, however, a single isolated polynucleotide sequence encoding the polypeptide sequence SEQ ID NO: 2 and no other nucleic acid or amino acid sequences that are proposed to correspond to the same structural and/or functional characteristics. Given the fact that the

specification fails to provide objective evidence of any additional sequences that are indeed species of the claimed genus it cannot be established that a representative number of species have been disclosed to support the genus claim.

9. Claims 4-8 and 10-11 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the polynucleotide of SEQ ID NO:1, does not reasonably provide enablement for polynucleotides encoding polypeptides comprising a CR-50 antibody recognition site of Reelin protein and neither a F-spondin domain nor a repeat site, comprising SEQ ID NO:2 and neither a F-spondin domain nor a repeat site, polypeptides as above comprising a deletion, substitution or addition of one or more amino acids, polypeptides encoded by degenerative nucleic acids, wherein the polypeptide binds to antibody CR-50, compositions that stimulate the assembly of Reelin protein and that are useful for diagnosis and/or treatment of diseases resulting from abnormally positioned neurons comprised the aforementioned nucleic acids. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The specification is insufficient to enable one skilled in the art to practice the invention as broadly claimed without undue experimentation. The factors relevant to this discussion include the quantity of experimentation necessary, the lack of working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims.

The skilled artisan readily recognizes that protein chemistry is an unpredictable area of biotechnology. Proteins with replacement of single amino acid residues may lead to both structural and functional changes in biological activity and immunological recognition, see in particular Skolnick et al., Trends in Biotech., 18(1):34-39, 2000. For example, Jobling et al, Mol. Microbiol., 1991, 5(7):1755-67 teaches a panel of single amino acid substitutions by oligonucleotide directed mutagenesis which produce proteins that differ in native conformation, immunological recognition, binding and toxicity. Thus, these references exemplify the importance of conserved structural components to both biological function and immunological recognition. The skilled artisan also recognizes that immunological responses depend upon the structural characteristics (conformation) of the particular protein (amino acid sequence) targeted and that variations in sequence may effect such structure and immunological recognition.

Instant specification discloses a CR-50 epitope designated as SEQ ID NO:2, corresponding to residues 230-346 of Reelin protein, see in particular p. 4, lines 11-18. However, the claims are drawn generically to polynucleotides encoding polypeptides comprising a CR-50 antibody recognition site of Reelin protein and neither a F-spondin domain nor a repeat site, comprising SEQ ID NO:2 and neither a F-spondin domain nor a repeat site, polypeptides as above comprising a deletion, substitution or addition of one or more amino acids, polypeptides encoded by degenerative nucleic acids and wherein the polypeptide binds to antibody CR-50. Additionally the claims recite compositions that

stimulate the assembly of Reelin protein and that are useful for diagnosis and/or treatment of diseases resulting from abnormally positioned neurons which comprise the aforementioned nucleic acids.

Thus, the claims are directed to polynucleotides encoding peptides with greater than single amino acid substitutions, deletions and insertions and to partial peptide fragments which bind CR-50 antibody. Yet the specification fails to teach alternative sequences other than SEQ ID NO:2 encoded by SEQ ID NO:1 and degenerate sequences thereof, capable of binding CR-50 antibody that corresponds to the claim recitations. There is no disclosure of those residues which may be replaced, modified, inserted or deleted without abrogating the disclosed immunological reactivity. Moreover, as pertinent in claims 10-11, the specification fails to teach such suitable compositions for stimulating the assembly of Reelin protein molecules or for providing a pharmaceutical for diagnosis or treatment of diseases resulting from abnormally positioned neurons.

At most the specification recognizes an epitope region which binds CR-50 antibody and which spontaneously forms a regular homopolymer via electrostatic interaction as disclosed at p. 4, lines 11-18. Furthermore, Reelin mutants are only recognized in mice and the model system is pertinent only to the Reelin phenotype which does not approximate all recognized abnormally positioned neurons but only those recognized as aberrantly positioned in Reelin animals, see for example Curran et al., Br. Res. & Br. Res. Reviews, 26(2-3):285-94, May 1998.

The specification does not enable the broad scope of the claims that encompass a multitude of analogs or equivalents because the specification does not teach which residues can or should be modified such that the polypeptides retain sufficient structural similarity to evoke immune responses or to provide for the required effects. The specification provides essentially no guidance as to which of the essentially infinite possible choices is likely to be successful and the skilled artisan would not expect functional conservation or immunological recognition among homologous sequences. Thus, applicants have not provided sufficient guidance to enable one skilled in the art to make and use the claimed derivatives in a manner reasonably correlated with the scope of the claims. The artisan recognizes that such structure is critical to antibody binding. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without such guidance, the changes which can be made and still maintain activity/utility is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See Ex parte Forman, 230 USPQ 546 (Bd. Pat. App. & Int. 1986).

Thus, in view of the lack of guidance, lack of examples, and lack of predictability associated with regard to producing and using the myriad of derivatives and fragments encompassed by the claims, one skilled in the art would be forced into undue experimentation in order to determine those peptides which correlate to the recitations of the claims, i.e., to define those residues capable of CR-50 monoclonal antibody binding, stimulating the assembly of

Reelin proteins or diagnosing or treating diseases associated with abnormally positioned neruons. Further the artisan would be required to confirm the peptides utility in the process of making and using a polypeptide capable of stimulating an antibody capable of binding reelin products, thus inhibiting Reelin function, see in particular Utsunomiya-Tate N., et al., PNAS, 97(17):9729-34, Aug. 15, 2000. Therefore, the enablement provided by the specification, in view of the skill in the art, is not commensurate in scope with the claims.

The ability to "make and test" is not the standard for an enabling disclosure. The instant specification fails to identify that structure which is required for the claimed biological . Moreover the activity of stimulating the assembly of a Reelin protein molecule, is not limited to mouse Reelin or to anti-Reelin antibody binding activity to which applicants refer within the specification. Neither are the diseases capable of diagnosis and/or treatment referenced by the claim as the specification suggests. The limitations of the specification cannot be read into the claims but must be recited thereby.

In the absence of guidance, a practitioner of the art of molecular biology would have to resort to a substantial amount of experimental trial and error to produce the peptides as claimed. This trial and error would constitute undue experimentation as there is no guidance as to which of the modifications would reasonably correspond to the structures and/or functions of the claims and therefore, the instant specification is not enabling for the full scope of the peptides claimed. The standard for an enabling disclosure is not one of making and testing and the claims constitute a "wish to know". Because there is no

reasonable expectation that any modification would either correspond both structurally and functionally, the experimentation is undue.

What is required is some degree of predictability as to those modifications that are appropriate. The instant specification fails to provide the requisite elements and thus one is not provided any expectation of antibody binding.

10. Claims 4-8 and 10-11 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claims contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The amended claims require antibody CR-50 binding. However, the specification is non-enabling with respect to this element because there is insufficient assurance that the antibody can be reproducibly isolated and/oris publicly available. While the antibody is recognized in the prior art, the antibody is required to make and use the invention as claimed. In particular, the peptides are in part defined by their testing positive for CR-50 immunoreactivity.

The specification lacks deposit information for the deposit of antibody CR-50. Because it is not clear that the antibody is definitively known and publicly available or can be reproducibly isolated from nature without undue experimentation and because the claims require the use of CR-50, a suitable deposit for patent purposes is required. Accordingly, filing of evidence of the public availability of the CR-50 antibody designated as a limitation within claims 4-8 and 10-11 is required. Without publicly available deposit of the above

antibody, one of ordinary skill in the art could not be assured of the ability to practice the invention as claimed. Exact replication of the antibody is an unpredictable event.

If the deposit is made under the provisions of the Budapest Treaty, filing of an affidavit or declaration by applicant or assignees or a statement by an attorney of record who has authority and control over the conditions of deposit over his or her signature and registration number stating that the deposit has been accepted by an International Depository Authority under the provisions of the Budapest Treaty and that all restrictions upon public access to the deposit will be irrevocably removed upon the grant of the patent on this application. These requirements are necessary when deposits are made under the provisions of the Budapest Treaty as the Treaty leaves this specific matter to the discretion of each State. Amendment of the specification to recite the date of deposit and the complete name and full street address of the depository is required.

If the deposits are not been made under the provisions of the Budapest Treaty, then in order to certify that the deposits comply with the criteria set forth in 37 CFR § 1.801-1.809, assurances regarding availability and permanency of deposits are required. Such assurance may be in the form of an affidavit or declaration by applicants or assignees or in the form of a statement by an attorney of record who has the authority and control over the conditions of deposit over his or her signature and registration number averring:

(a) during the pendency of this application, access to the deposits will be afforded to the Commissioner upon request;

(b) all restrictions upon the availability to the public of the deposited biological material will be irrevocably removed upon the granting of a patent on this application;

(c) the deposits will be maintained in a public depository for a period of at least thirty years from the date of deposit or for the enforceable life of the patent of or for a period of five years after the date of the most recent request for the furnishing of a sample of the deposited biological material whichever is longest; and

(d) the deposits will be replaced if they should become nonviable or non replicable.

In addition, a deposit of biological material that is capable of self-replication either directly or indirectly must be viable at the time of deposit and during the term of deposit. Viability may be tested by the depository. The test must conclude only that the deposited material is capable of reproduction. A viability statement for each deposit of a biological material not made under the Budapest Treaty must be filed in the application and must contain:

1) The name and address of the depository;

2) The name and address of the depositor;
3) The date of deposit;
4) The identity of the deposit and the accession number given by the depository;
5) The date of the viability test;
6) The procedures used to obtain a sample if the test is not done by the depository; and
7) A statement that the deposit is capable of reproduction.

As a means for completing the record, applicant may submit a copy of the contract with the depository for deposit and maintenance of each deposit.

If the deposit was made after the effective filing date of the application for patent in the United States, a verified statement is required from a person in a position to corroborate that the antibody described in the specification as filed is the same as that deposited in the depository. Corroboration may take the form of a showing of a chain of custody from applicant to the depository coupled with corroboration that the deposit is identical to the biological material described in the specification and in the applicant's possession at the time the application was filed.

Applicant's attention is directed to In re Lundack, 773F.2d. 1216, 227 USPQ 90 (CAFC 1985) and 37 CFR § 1.801-1.809 for further information concerning deposit practice.

Claim Rejections - 35 USC § 102

11. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) do not apply to the examination of this application as the application being examined was not (1) filed on or after November 29, 2000, or (2) voluntarily published under 35 U.S.C. 122(b). Therefore, this application is examined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

12. Claims 4-8 and 10-11 are rejected under 35 U.S.C. 102(b) as being anticipated by de Bergeyck et al., J. of Neurosci. Methods, 82:17-24, 1998.

DeBergeyck et al., teach peptides useful in the generation of various antibodies to the mouse Reeler peptide. As in the abstract,

"Reelin, the extracellular matrix protein defective in reeler mutant mice, plays a key role during brain development. We therefore raised antibodies directed against various reelin epitopes in order to facilitate biochemical and cell biological studies of this important molecule. Homozygous reeler mice with a large deletion of most of the reelin gene were immunized with fusion proteins and carrier-coupled peptides corresponding to parts of the reelin sequence. Monoclonal antibodies were produced using classical procedures, screened using ELISA and–or western blot prepared with the antigen, and tested by immunohistochemistry and immunoprecipitation assays to detect endogenous reelin. The labeling of Cajal–Retzius cells in the embryonic mouse telencephalon was selected as criterion for positivity in immunohistochemistry. A total of 11 monoclonal antibodies were obtained, providing useful additions to the widely used antibody CR-50. Five are directed against the N-terminal part of reelin, among which three recognize the region that has significant similarity with F-spondin, and two are specific for hinge region located downstream from the F-spondin similarity region and upstream from the reelin repeats. Six antibodies are directed against the C-terminal part of reelin, among which one anti-peptide antibody recognizes the highly basic C-terminal segment. Antibodies against the N-terminal region stain well in immunohistochemistry. By comparison, the labeling of embryonic Cajal–Retzius cells with antibodies directed against the C-terminal region is weaker, suggesting that this part of the molecule might be modified or not be as readily accessible in the tissue as the N-terminus."

In particular, the peptide immunogens are represented as in Figure 1B p. 18. Applicant's specification notes that the CR-50 recognition site is within residues 230-346 of Reelin. Peptide H164-496 is noted to be deleted in both the

F-spondin region as well as the C'terminal repeat region domains. As the peptide comprises residues 230-346, comprising the CR-50 eptiope region, it would bind the CR-50 antibody. The polynucleotides encoding the same residues shares identity and/or similarity to SEQ ID NO:1. Further the reference teaches analysis of the antibody specificity using peptides 164-405, 164-371 and 164-245, see in particular p. 22, columns 1-2, *3.3. Anti-protein H.* Thus, the polynucleotides encoding the peptide fragments anticipate the claimed compositions.

Applicants argue in the response of 3-01-04 that the art does not meet the claim limitations in that the H164-496 peptide is only missing a portion of the F-spondin domain.

Applicants arguments have been fully considered but are not persuasive. Applicant's concede that the F-spondin region corresponds to amino acids 28-190 of Reelin. While it is agreed that the H164-496 peptide only comprises a portion (27 amino acids) of the F-spondin domain, such does not correspond to having an F-spondin domain. Moreover, the claims are directed to deletion, substitution and addition mutants. At the very least the H164-496 mutant may correspond to such recitations. The peptide does not comprise a F-spondin domain because the domain is not included in full and the mutant may further correspond to a mutant lacking any of an F-spondin domain while containing a 27 amino acid addition. Thus, the rejection is maintained.

Claim Rejections - 35 USC § 103

13. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

14. Claims 4-8 and 10-11 are rejected under 35 U.S.C. 103(a) as being unpatentable over de Bergeyck et al., J. of Neurosci. Methods, 82:17-24, 1998, Nakajima et al., PNAS 94:8196-201, July 1997 and Miyata et al., J. of Neurosci., 17(10):3599-3609, 1997.

de Bergeyck et al., teach as set forth above. In particular, DeBergeyck et al., teach peptides useful in the generation of various antibodies to different portions of the mouse Reeler peptide for the purpose of providing diganostic reagents with the advantage of binding specific regions of the molecule to aid in deciphering the function of the different portions of the peptide within the host.

De Bergeyck et al., teach peptides comprising the CR-50 region as useful for the stimulation of antibodies reactive thereto. The H164-496 comprises the CR-50 domain but lacks a full F-spondin domain and lacks any portion of the repeats.

de Bergeyck et al., does not teach a specific peptide immunogen consisting of the CR-50 epitope region and thus containing none of the F-spondin domain and none of the repeat site. However, de Bergeyck et al., notes the desire to generate various antibodies specific to different portions of the mouse Reeler peptide for the purpose of providing diagnostic reagents with the advantage of binding specific regions of the molecule to aid in deciphering the function of the different portions of the peptide within the host. The reference also teaches testing with peptides of residues 164-405, 164-371 and 164-245.

Nakajima et al., teach antibody CR-50 generated via immunization with homogenates of normal embryonic brain, see in particular abstract. Nakajima notes that it is still unclear whether Reelin, especially the CR-50 epitiope region is indeed responsible for the reeler phenotype in vivo. However, Nakajima notes that injection of the antibody in the embryonic stage is capable of disrupting the normal pattern of development in the embryo converting it to the phenotype of the reeler mutant. Nakajima notes this finding evidences that the CR-50 epitope plays a central role in this function, see in particular abstract.

Miyata et al., teach that the CR-50 antibody regulates Purkinje cell alignment within the CNS in an in vitro model system, see in particular abstract. Further Miyata notes that the study reveals important steps downstream of reelin, see in particular p.3608, column 2, last paragraph. Miyata notes that the in vitro

assays are useful for assessment of the scrambler phenotype using the CR-50 antibody. In additon CR-50 is noted to be useful for functional experiments in vivo.

Thus, one of skill in the art would be motivated to produce a pepetide consisting of the CR-50 epitope peptide to make CR-50 epitope specific antibodies capable of blocking the noted reeler phenotype as suggested by Nakajima and Miyata. One of skill in the art would expect success using such techniques given the high skill in the art of making antibodies specific to various peptide regions and the teachings of Miyata and Nakajima that it is the CR-50 epitope that directs the reeler phenotype. The antibody so generated would provide for the advantages of CR-50 in functional testing within the in vitro and in vivo model systems. Thus, the cumulative reference teaching render the claimed invention obvious to one of skill in the art.

Status of Claims

15. No claims are allowed.

16. Any inquiry of a general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Papers relating to this application may be submitted to Technology Center 1600, Group 1640 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). Should applicant wish to FAX a response, the current FAX number for Group 1600 is (703) 872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through

Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sharon L. Turner, Ph.D. whose telephone number is (571) 272-0894. The examiner can normally be reached on Monday-Friday from 8:00 AM to 4:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback can be reached at (571) 272-0961.

Sharon L. Turner, Ph.D.
July 12, 2004